RANDOMIZED SURGICAL TRIALS AND "SHAM" SURGERY: RELEVANCE TO MODERN ORTHOPAEDICS AND MINIMALLY INVASIVE SURGERY

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ABSTRACT

Surgical techniques are constantly changing and evolving, though research trials supporting the value of a specific surgical intervention are often limited by the lack of a legitimate control group. In surgical trials, the use of a placebo, or a "sham" surgery, is controversial. This article explores the debate regarding the use of sham surgeries and summarizes the few surgical studies that have used them. Arguments for and against their use in research are presented.

INTRODUCTION

In general, new surgical procedures are developed by a single surgeon or a small group of surgeons. These individuals then employ the new procedure on their patients, observe the results, and report them either as prospective or retrospective studies. This approach does not allow comparison of one procedure with others, or with a sham procedure, or (in most instances) with nonoperative treatment. Acceptance of new procedures is based on their perceived value relative to previously accepted treatments. This process can be powerfully influenced by the enthusiasm, skill, and prominence of the surgeon reporting the results and by their selection of patients for treatment. Reitsma observed that "In a climate where surgeons introduce experimental techniques without formal research preceding such innovations, surgical research is an ill-defined and elusive entity."[16]

The gold standard of clinical research is the double-blind randomized placebo-controlled trial, yet very few surgical procedures are subjected to this form of investigation.[1,18] Studies that are done in other fashions are often criticized for failing to provide the true answer regarding the usefulness of a surgical procedure. In a randomized controlled trial there is a control group to which other treatment arms are compared. The control group is treated with a placebo in most medical specialty studies and pharmacology studies. However, in surgical trials, the use of a placebo, or a "sham" surgery, is controversial. In particular the question arises: When is it ethical, if ever, to perform sham surgery? The purpose of this article is to review the debate regarding the use of sham surgeries and summarize the few surgical studies that have used them. Arguments for and against their use in research will be presented.

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BACKGROUND

The field of surgery has advanced at an unbelievable pace over the last several decades. No one would have believed 50 years ago that you could remove tumors from the brain using computer guidance, replace joints with titanium implants through three-inch incisions, or change a person's vision with the use of a laser. Advances in surgical equipment and technology have been driving the advances in surgery. The art and practice of surgery began as a way to save lives in critical situations. However, today the vast majority of surgical procedures are done on an elective basis to improve quality of life. Traditionally, surgeries to treat acute or chronic disease have been accepted based on retrospective cohort analyses that are compared to historical nonoperative series. Sham surgery controlled trials have not been encouraged or performed regularly. A placebo controlled trial was inconceivable at the inception of surgery, as surgical intervention was performed only in "life or death" situations, and this remains true for some cases today. For example, one would not consider a sham surgery controlled trial involving irrigation and debridement of an infected joint.

THE PLACEBO EFFECT AND SHAM SURGERY

The problem for most surgical studies is determining how much of the effect of surgery is from the procedure itself and how much is placebo effect. As opposed to using a nonoperative control group, the benefit of using a sham surgery control in surgical trials is that sham surgery equalizes the placebo effect of surgery.

Beecher first described the placebo effect of surgery in a classic paper following a randomized trial of internal mammary artery ligation versus a sham operation for angina pectoris back in 1959.[9,17] The placebo response for surgery mimics that seen for other therapeutic interventions, accounting for up to 35 percent of the response.[10] Part of the placebo effect is thought to be due to the surgeon-patient relationship.[9,10] Equalizing as many variables as possible for the patient's treatment experience allows for the best understanding of the direct effect of the surgical procedure itself.

There are several core ethical principles at stake at the center of the debate regarding the use of sham surgery in surgical trials. In 1947, the Nuremberg Code put forth a statement regarding the appropriate practice of research on human subjects.[19] The Nuremberg Code decreed that all research should avoid any unnecessary physical or mental suffering, and the degree of risk to be taken should never exceed the humanitarian importance of the problem to be solved by the experiment.[19] In 1964, the Declaration of Helsinki reiterated many of the principles of the Nuremberg Code and expounded on them. This included the statement that the "concern for the interests of the subject must always prevail over the interests of society and science."[20] Finally, in the Belmont Report of 1979, the National Commission for the Protection of Human Subjects put forth the three basic principles of respect for persons, beneficence, and justice.[15] This commission recognized the difficulty of balancing the importance of advancing science against the risks and benefits to study participants, stating there is "difficulty of making precise judgments" regarding the risk/benefit ratio of research protocols.

Certainly, trying to balance the benefit of sound study design, elimination of placebo effect, and truly studying a surgical procedure is valuable. However, making a non-therapeutic incision on a subject's skin definitely infringes upon the concept of "do no harm." Also, the risks of surgery are not benign. They include the possibility of bleeding, infection, antibiotic treatment to prevent infection, and the risk of undergoing an anesthetic. How do we balance these risks against the tremendous advantage of a sham controlled study designed to answer socially important scientific questions?

There have been very few sham controlled surgical trials to date. In 1959, Cobb published a study showing no difference in improvement between patients undergoing internal mammary artery ligature versus a sham operation for treatment of angina pectoris.[17] In recent years, two studies were done to evaluate the intracranial implantation of fetal neural cells for Parkinson's disease.[3,4] These studies had some of the study patients randomized to a sham operation that required simulating all aspects of the surgery, including the drilling of burr holes on the skull under anesthesia. In the field of orthopaedics, Moseley et al. in 2002 evaluated the effectiveness of arthroscopic surgery for arthritis of the knee.[1] In this study, one group received a full arthroscopic debridement, one group underwent arthroscopic lavage with irrigation fluid alone, and the last group had three one-centimeter sham incisions but no actual procedure performed. This study concluded that arthroscopic surgeries done for advanced arthritis were no more effective than the sham operation.

The Parkinson's sham surgery trials and the Moseley knee arthroscopy study stimulated several commentaries on the ethics of sham surgery in research.[2,5,6,7] Macklin identifies the fact that sham surgery has no potential benefit for the patient and violates the principle of minimizing harm to the patient as one of the major ethical issues presented by sham surgery use in surgical research.[2,15,19,20] The declaration of Helsinki states that "every patient, including those of the control group—if any, should be assured of the best proven diagnostic and therapeutic method."[20] To avoid this additional and nontherapeutic risk to the patient, the sham surgery could be thrown out and a control group who receives nonoperative or less risky management could be used. In contrast, Stock disagrees with the argument that no clinical benefit is gained by participants who receive a sham operation.[24] They receive pain medicine, frequent attentive follow-up, exercise programs, counseling, and the placebo effect of surgery.

MEDICAL VERSUS SURGICAL RESEARCH

According to Miller, a distinction should be made between the ethics of clinical research and the ethics of daily medical care.[8] Sham surgery controls have been criticized since they counter the basic tenet of medicine to "do no harm." However, this is not treating these surgical trials for what they are: Research. Miller suggests that it is not fair to impart the ethics of daily clinical medicine to research trials, and offers that sham surgeries should be viewed in the same spectrum as additional blood draws, radiographs, lumbar punctures, and biopsies - all things done regularly in accepted medical trials every day. Others counter that sham controls are different from medical placebo controls due to their substantial additional risks that are unique to surgery, such as anesthesia, bleeding, infection, and additional pain.[22] An additional harm is done to patients as well. The patient, having just undergone an operation, also must then be actively deceived. One author, who happens also to be a surgeon, has suggested that the physician who performed the operation must then be removed as much as possible from the postoperative care of the patient

to eliminate the need for the surgeons to participate in this deception.[22]

SHAM SURGERY: RISKS AND BENEFITS

The next major issue concerns finding the appropriate balance between the risks and benefits of research involving sham surgery. Some authors argue that the risk of sham operations cannot be justified regardless of the benefit, but many others agree that the risk/benefit ratio requires extremely careful analysis on a case-by-case basis.[6,8,11,22,23,24,27] Several factors contribute to this analysis. London and Kadane suggest closely examining the importance of the sham control.[24] If there is acknowledged debate regarding the best treatment for an illness and if that debate centers on no treatment versus surgical treatment, then a sham surgery could be justified. For instance, these authors did not feel that there was evidence to support sham surgery in the Moseley knee arthroscopy trial because a previous study had already shown no benefit of lavage over placebo.[24]

In addition, there may be substantial differences in the risks involved in various sham operations, as is the case with the Parkinson's trial and the knee arthroscopy trial mentioned previously. One required creating burr holes in the cranium, while the other used three one-centimeter stab incisions about the knee. One could argue that making an extraneous skin incision is little riskier than bronchoscopy, endoscopy, multiple blood draws, or other invasive procedures readily accepted in other trials.[8]

Moreover, the societal benefits of sham controlled trials could be great. Sham surgery has the potential benefit of saving society from the financial burdens of unproven operations.[23] For instance, the Moseley study concluded that knee arthroscopy for advanced arthritis, performed between 5000 and 6500 times a year at a cost of approximately $5000 per procedure, was no more effective than placebo.[1] Testing the efficacy of expensive surgical and medical interventions with sham controls, as in the Moseley study, could have a dramatic impact on future medical costs. Lastly, sham operations may be the only option to truly determine whether a benefit from surgical intervention truly exists.

SURGICAL TRIALS: INFORMED CONSENT

The third major issue for sham surgeries involves enrolling and consenting patients for participation. The informed consent procedure for trials that involve sham operations is imperfect. Regardless of the detail in which patients are counseled that sham surgery may be performed, the "therapeutic misconception" still exists for many patients who are desperate for treatment.[8] This was a significant issue for the stem cell research trials done for Parkinson's disease, which is a terminal illness. However, the Parkinson's patients may be no less desperate than cancer patients consenting for placebo controlled drug therapy trials that are an accepted part of cancer chemotherapy research.

Another important issue is dealing with the very sensitive nature of human subject experimental research among the general public. Media attention to both the Moseley knee arthritis study, as well as the recent political debate regarding stem cell research such as the Parkinson's disease trial, has raised public awareness about the use of human subjects in research. Leeds has advocated that social aspects of sham surgery should be explored since there is an "inherent aversion" to sham operations in the general public.[26] Such education efforts would potentially include forums that bring forth opinions of physicians, former subjects in sham controlled trials, and representatives of the public to show that the medical community is concerned about public opinion regarding sham operations. Numerous operative interventions are becoming relatively routine and accepted based on minimal or shaky evidence of patient improvement. Every measure necessary should be taken to explore the appropriate use of potentially invaluable sham-controlled analyses.

Taking all these factors into account is necessary to determine the usefulness of and justification for placebo-controlled surgical trials. Emmanuel and Miller have suggested that one of four criteria should be met before placebo-controlled trials are required from a scientific standpoint.[25] These conditions are: A high placebo response rate, a condition that is chronic with a waxing/waning course, a condition for which existing therapies are only partly effective or have serious side-effects, or a relatively infrequent condition.

APPLICATION TO ORTHOPAEDIC RESEARCH: MINIMALLY INVASIVE SURGERY

Abundant possibilities exist in the field of orthopaedic surgery for such research. We like to believe that the surgical procedures we perform on patients offer a better outcome than that of nonoperative treatment or older surgical techniques. Depending on the condition, the true results of operative treatment are perhaps debatable; such uncertainties are more prevalent than we care to think about. Orthopaedics, as much as any other discipline in medicine, is driven by forces from technology and industry. Much of the focus in recent years has centered on less invasive procedures. Such well-established and successful interventions as total hip replacement, rotator cuff surgery, total knee replacement, shoulder stabilization surgery, and others are being done through surgical approaches that mini-

mize skin incisions. The advocates of these procedures cite decreased recuperation time, decreased morbidity, decreased pain, and fewer days of hospitalization as advantages of these procedures. Since these techniques are newer than more traditional and more extensive open techniques, comparable long-term results are not available. In addition, the traditional techniques continue to evolve and improve as well.

It would be advantageous to directly compare results of minimally invasive surgery to more traditional techniques. The ideal way to do this would be a randomized blinded clinical trial to remove patient and surgeon bias that might affect outcomes. There are significant difficulties with such a trial, however. First, the surgeon must believe there is a real question to be answered and that one treatment is not better than the other, commonly referred to as clinical equipoise. Secondly, increasing numbers of patients today are interested in the potential benefits of minimally invasive surgery. Naturally, if you ask a patient if they would prefer three one-centimeter incisions and to go home the same day as surgery, versus a four-inch incision and a stay overnight in the hospital, most patients will opt for the former. Optimally, this could be tested through a blinded randomized trial with all patients receiving the same skin incisions, regardless of surgical technique used. This would blind the patient, the clinician doing the follow-up, and others to the exact method used. Indications for surgery would need to be standardized and every effort made to eliminate selection bias for a trial of this nature. Minimally invasive surgeries have a significant learning curve and many surgeons select technically easier cases on which to use these techniques. Such bias must be eliminated to truly understand how these new and old techniques compare. The obvious obstacle to this kind of design is that extra skin incisions would be placed on patients who are really undergoing the minimally invasive procedure. Does this additional incision truly put them at greater risk? This is unclear, but a human subjects' office would likely have a hard time with this design. However, as we move forward with better research in the surgical specialties, issues such as these should be tackled if we truly want to decipher what is ultimately best for patients.

SUMMARY

Given the ethical background reviewed above, the field of orthopaedic surgery would benefit from further surgical trials that incorporate some element of sham surgery. Conferences around the globe abound with symposia debating the merits of various surgical techniques, mostly centered on how "invasive" a procedure appears. These debates center around some of the most commonly performed orthopaedic procedures, such as rotator cuff repairs, shoulder stabilization, and hip and knee replacements. The means to providing answers are available, but come at the cost of sham incisions and sham surgery. Many years ago such surgical research eliminated a common surgical intervention, internal mammary artery ligation, from the treatment algorithm for chest pain. One can only imagine what other surgical interventions we might change with further such research today.

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